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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	17

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/484,331	Applicant(s) HARRINGTON ET AL.	
	Examiner Ram Shukla	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133)
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *62-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *13*
18)☐ Interview Summary (PTO-413) Paper No(s). _____.
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

1. The request filed on 1-18-01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/484331 is acceptable and a CPA has been established. An action on the CPA follows.

2. Applicants remarks regarding the issues discussed in the interview of 1-5-01 is recorded.

3. Amendments filed 1-18-01 have been entered.

4. Claims 58-61 have been canceled.

5. Claims 62-68 have been entered.

6. Claims 62-68 are pending in the instant application.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 62-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappel SC (US 5,272,071, 12-21-1993; EP0779362 A1, 6-18-1997) in view of Dimaio et al (WO9220784, 11-26-1992).

Claimed invention is drawn to a method of drug discovery wherein the expression of an endogenous gene in a cell is activated due to integration of a vector, the cell is cultured under conditions that favor expression of said endogenous gene, the cells are screened for the phenotype related to the endogenous gene and a cell that displays desired phenotype is exposed to one or more candidate compounds and a compound is selected based on the effect of the compound on the desired phenotype.

At the time of the invention, Chappel taught a method of endogenous gene activation and expression modification. This art also taught to specifically express specific genes present but normally silent in a cell of choice and that the method resulted in expression of an endogenous gene from complete genomic sequences of the endogenous gene. Chappel's method provided a method wherein the expression of an endogenous gene was activated by

inserting DNA regulatory seqments and or amplifying segments into the genome of a stable cell line upstream of or proximal to the native gene of interest (see abstract and entire document of US 5,272,071). The construct also contained selectable marker and amplifiable marker for amplification of the gene expression and selection of cells that express the endogenous gene (see lines 51-58 on page 3 to lines 1-55 on page 4 of EP0779362 A1, 6-18-1997). As an example, Chappel taught the expression of thyrotropin beta in GH3 cells, a rat tumor cell line (see lines 54-58 on page 10 EP0779362 A1, 6-18-1997). On pages 11-14, Chappel teaches characterization and selection of cells, and culture of the cells expressing thyrotropin beta. Chappel et al do not teach the step of testing compounds using these cells(EP0779362 A1, 6-18-1997). It is noted that both the EP document as well as the US document are the same and therefore pertinent portions of only one document has been cited.

Dimaio et al teaches a keratinocyte cell line which expresses human papillomavirus E5 gene and further teach that such cell lines are useful as a drug screen to identify compounds that inhibit the action of the E5 gene (see the abstract). Diamaio et al further discloses that keratinocytes transformed by HPV16 E5 gene can be used to establish a screen to identify compounds that inhibit E5 action wherein such compounds may alter growth properties of altered biochemical characteristics that these cells may express in cell culture (see the last paragraph on page 17).

At the time of the invention, it would have been obvious to use the GH3 cells expressing an endogenous gene, for example, expressing thyrotropin gene or any other endogenous gene, whose expression was activated in these cells in drug screening assays for identifying compounds that would have altered the characteristics of the cell expressing the endogenous gene or the biochemical properties of the protein encoded by the endogenous gene with a reasonable expectation of success. It is noted that at the time of the invention an artisan would have been motivated to use such cells expressing (increased expression) endogenous genes that are usually silent are expressed at low levels because such cells would have provided sufficient amount of protein to test the activity and also because the protein produced would have altered the characteristics of the cell which would have helped the screening assay. As taught by Dimiao cell lines expressing a protein of interest were used for drug screening at the time of the invention.

Regarding claims 63-65, growing cells in reduced serum medium (for example see claim 5 of Magdalena G. et al. US US 4254226 A , 3-3-1981) and concentrating or purifying proteins

from the culture media are routine steps while expressing and producing a recombinant protein in a cell line.

9. Claims 62-~~78~~ 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Treco et al (Treco Douglas, 5,641670, 6-27-1997) in view of Dimaio et al Dimaio et al (WO9220784, 11-26-1992).

Claimed invention (claims 62-27) is drawn to a method of drug discovery wherein the expression of an endogenous gene in a cell is activated due to integration of a vector, the cell is cultured under conditions that favor expression of said endogenous gene, the cells are screened for the phenotype related to the endogenous gene and a cell that displays desired phenotype is exposed to one or more candidate compounds and a compound is selected based on the effect of the compound on the desired phenotype. Claim 68 limits the method to non-homologous recombination.

Treco et al teach vectors for protein production and delivery, for example, the vector of figure 8 which has a transcription regulatory sequence, hGH exon 1, dhfr gene and origin of replication. This patent also teaches a cell wherein the vector is integrated, and wherein an endogenous gene is over-expressed in said cell by up regulation of the gene by transcriptional regulatory sequence on said vector construct (see figures, examples and columns 1, lines 56-67 continued in columns 6 for summary).

Capecchi reviews the state of the art of gene replacement by homologous recombination. Capecchi notes, "Regrettably, such targeted replacement occurs only in a small fraction of the treated cells. More often, the targeting vector inserts randomly at non-matching sites or fails to integrate at all. We must therefore sort through the cells to identify those in which targeting has succeeded. Approximately, one in a million treated cells has the desired replacement" (see last paragraph in column 3 on page 56 continued in the first paragraph in column on page 57). He further discusses the methods to screen the cells which express the targeted gene.

Dimaio et al teaches a keratinocyte cell line which expresses human papillomavirus E5 gene and further teach that such cell lines are useful as a drug screen to identify compounds that inhibit the action of the E5 gene (see the abstract). Diamaio et al further discloses that keratinocytes transformed by HPV16 E5 gene can be used to establish a screen to identify compounds that inhibit E5 action wherein such compounds may alter growth properties of

altered biochemical characteristics that these cells may express in cell culture (see the last paragraph on page 17).

It is noted that the vector in claim 62 is not limited by the presence of any particular components are same in the Treco method and the claimed method because the vectors and methods of the claimed method use the term "comprising" which would indicate that any other sequence element can be present. Although, the claimed method of the instant application (claim 68) recites that the vector integrates into the genome of the cell by non-homologous recombination', as noted by Capecchi, even when homologous sequences are included in a vector for targeted activation of an endogenous gene, the vector integrates in the genome of the majority of the cells by non-homologous recombination because that is the preferred method of integration of an exogenous DNA in a cell. While the method of Treco is to homologous recombination method, it would include majority of cells wherein the vector would have integrated randomly and then a cell with proper expression product has to be screened which would be the same as claimed in the instant application. In the event that the claimed protein is not identical to that disclosed by Treco, it is considered that, as noted above, integration of the Treco et al construct will occur by random integration and if integrated 3' to an endogenous promoter would expression the coding sequences downstream of the site of integration.

At the time of the invention, it would have been obvious to use the cells expressing an endogenous gene, for example, expressing human EPO gene or any other endogenous gene, whose expression was activated in these cells in drug screening assays for identifying compounds that would have altered the characteristics of the cell expressing the endogenous gene or the biochemical properties of the protein encoded by the endogenous gene with a reasonable expectation of success. It is noted that at the time of the invention an artisan would have been motivated to use such cells expressing (increased expression) endogenous genes that are usually silent are expressed at low levels because such cells would have provided sufficient amount of protein to test the activity and also because the protein produced would have altered the characteristics of the cell which would have helped the screening assay. As taught by Dimiao cell lines expressing a protein of interest were used for drug screening at the time of the invention.

Regarding claims 63-65, growing cells in reduced serum medium (for example see claim 5 of Magdalena G. et al. US US 4254226 A , 3-3-1981) and concentrating or

purifying proteins from the culture media are routine steps while expressing and producing a recombinant protein in a cell line.

Response to Arguments

Applicant's arguments regarding the rejections in the final office action of 11-17-200 are moot in view of the new ground(s) of rejection.

10. No claim is allowed.

Applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c). For instruction, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Kay Pinkney whose telephone number is (703) 305-3553.

Ram R. Shukla, Ph.D.

Karen M. Hauda

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